



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

EAACI Guidelines on Allergen Immunotherapy

Citation for published version:

Muraro, A, Roberts, G, Halken, S, Agache, A, Angier, L, Fernandez Rivas, M, Gerth van Wijk, R, Jutel, M, Lau, S, Pajno, G, Pfaar, O, Ryan, D, Sturm, GJ, Van Ree, R, Varga, EM, Bachert, C, Calderon, MJ, Canonica, GW, Durham, SR, Malling, HJ, Wahn, U & Sheikh, A 2019, 'EAACI Guidelines on Allergen Immunotherapy: Executive Statement', *Allergy*. <https://doi.org/10.1111/all.13420>

Digital Object Identifier (DOI):

[10.1111/all.13420](https://doi.org/10.1111/all.13420)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Allergy

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



PROF. GRAHAM C ROBERTS (Orcid ID : 0000-0003-2252-1248)

DR. IOANA AGACHE (Orcid ID : 0000-0001-7994-364X)

DR. ROY GERTH VAN WIJK (Orcid ID : 0000-0002-9608-8742)

PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)

DR. DERMOT RYAN (Orcid ID : 0000-0002-4115-7376)

DR. EVA M VARGA (Orcid ID : 0000-0003-3936-5608)

PROF. CLAUS BACHERT (Orcid ID : 0000-0003-4742-1665)

Article type : Editorial

EAACI Guidelines on Allergen Immunotherapy: Executive Statement

Authors: Muraro A^{1*}, Roberts G^{2-4*}, Halken S⁵, Agache A⁶, Angier L⁷, Fernandez–Rivas M⁸, Gerth van Wijk R⁹, Jutel M¹⁰, Lau S¹¹, Pajno G¹², Pfaar O^{13,14}, Ryan D¹⁵, Sturm GJ¹⁶, van Ree R¹⁷, Varga E-M¹⁸, Bachert C¹⁹, Calderon M²⁰, Canonica GW²¹, Durham SR²⁰, Malling HJ²², Wahn U²³, Sheikh A²⁴.

*Denotes equal contribution

Affiliations:

1. Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Padua, Italy
2. The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK
3. NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
4. Clinical and Experimental Sciences and Human Development in Health Academic Units, Faculty of Medicine, University of Southampton, Southampton, UK
5. Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark
6. Transylvania University Brasov, Faculty of Medicine, Department of Allergy and Clinical Immunology, Brasov, Romania

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13420

This article is protected by copyright. All rights reserved.

7. Primary Care and Population Science, Faculty of Medicine, University of Southampton, Southampton, U.K.
8. Allergy Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain
9. Section of Allergology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
10. ALL-MED Medical Research Institute, Wroclaw Medical University, Poland
11. Department of Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany
12. Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy
13. Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;
14. Center for Rhinology and Allergology, Wiesbaden, Germany
15. Usher Institute of Population Health Sciences and Informatics, University of Edinburgh Medical School, Edinburgh, UK
16. Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria; Outpatient Allergy Clinic Reumannplatz, Vienna, Austria
17. Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
18. Dept. of Paediatric and Adolescent Medicine, Respiratory and Allergic Disease Division, Medical University of Graz, Graz, Austria
19. Upper Airways Research Laboratory and ENT-Department, University Hospital Ghent, Ghent, Belgium
20. Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London, London, UK
21. Personalized Medicine Asthma & Allergy Clinic, Humanitas University and Research Hospital, Milano, Italy
22. Danish Allergy Centre, University of Copenhagen, Copenhagen, Denmark
23. Department for Pediatric Pneumology and Immunology, Charité Universitätsmedizin, Berlin, Germany
24. Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK

Correspondence: Antonella Muraro, Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, University of Padua, Via Giustiniani 3, 35128 Padua, Italy Tel.: +39-049-821-2538 Fax: +39-049-8218091 E-mail: muraro@centroallergiealimentari.eu

Short title: EAACI AIT Guidelines

Key words: allergen immunotherapy, allergy, allergic rhinoconjunctivitis, venom allergy,

food allergy, prevention

Abbreviations:

AIT Allergen Immunotherapy

RCT Randomized controlled trials

The allergist's community has recently celebrated 100 year of Allergen Immunotherapy (AIT). Unfortunately the implementation of this treatment is still impaired by some challenges. With the diversity of definitions, methodology and different allergen products used, research studies have produced conflicting outcomes. This has resulted in confusion about the benefits and risks of AIT amongst policymakers and professionals, as well as in the variable availability of AIT products, regulation and reimbursement policies globally. In 2015 EAACI initiated the AIT Guidelines project as part of the Presidential plan in order to settle the controversies. The result has been a rigorous process of guideline development (1) in order to inform and facilitate high quality clinical practice for AIT. The Guidelines are based on some key pillars: an evidence-based approach, involvement of multidisciplinary and multiprofessional groups, recommendations centred on the patient, highlighting the benefits and harms of AIT. In the development process *accountability to evidence* meant paying attention to *transparency* and *independency* of the process. *Rigour of development* was reflected in the provision of search strategy details, a description of the process for external review and a plan for future update of the guidelines. Although these Guidelines were funded by EAACI, the funder had no influence on the guideline production process, its contents nor on the decision to publish. Taskforce members' conflicts of interest were declared and taken into account. Final decisions about strength of evidence for recommendations were checked by the methodologists who had no conflicts of interest in this area.

The process of producing these guidelines has involved recognition of the importance of following a structured process (2), created a valuable opportunity for clinicians, researchers, methodologists and patient representatives to work together, and has allowed a shared appreciation of the need to also consider implementation considerations so the benefits of AIT can be safely realized by our patients. We have had to address some challenges, shared with other disciplines (3), that it would be useful to discuss. *Firstly*, the evidence-based approach is often seen as too demanding so we adopted a user-friendly approach to facilitate appraisal of the key evidence to generate recommendations (4). *Secondly*,

guidelines are often seen as very narrow so we carefully considered and incorporated the views of other stakeholders in formulating recommendations. *Thirdly* a criticism was raised as to whether the time, effort and expense involved were worthwhile and whether it would make a difference to the ultimate recommendations. We suggest that a rigorous and transparent process provides good value by adding confidence on the validity of the recommendations for practicing clinicians.

Approach to generating the Guidelines

The EAACI AIT Steering Group decided to employ the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach to generate the AIT guidelines (2), as this was considered best tailored to generate guidelines for clinicians. This framework ensures appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations and steps to minimize the risk of bias at each step of the process.

The initial full range of clinical questions that were considered important for the guidelines were rationalized into an over-arching question for each guideline, namely the effectiveness, safety and cost-effectiveness of allergen immunotherapy for allergy prevention, food allergy, allergic rhinitis, asthma, and venom allergy. These questions were then pursued through developing systematic reviews led by independent methodologists. We continued to track relevant evidence after our systematic review cut-off dates.

We graded the strength and consistency of key findings from the systematic reviews and, where possible and appropriate, performed meta-analyses using random-effects models to take into account the heterogeneity of findings. This approach was the basis to formulate evidence-based recommendations for clinical care. The Oxford Centre for Evidence-based Medicine (4) methodology was used as a practical approach that could be readily utilized by the EAACI Taskforce members. This involved both formulating the recommendations and detailing the strength of evidence underpinning each recommendation. Where the systematic reviews did not cover the clinical area, we took a hierarchical approach to review other evidence until we could formulate a recommendation as follows: (i) other systematic reviews on the subject to see if they provided any further clarity on the topic; (ii) randomized controlled trials (RCT) within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach within the Taskforce. This evidence was graded and clearly labelled in the recommendation tables. When there were insufficient pediatric data, we extrapolated from the adult recommendation where it was biologically

likely that the intervention would also be effective in children, but in so doing, the recommendation was downgraded by at least one level.

A draft of each Guideline was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds. Additionally, each draft guideline was made available on the public domain of the EAACI Website for a three week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by Taskforce members and final revisions were made in the light of the feedback received.

How to use the Guidelines

These Guidelines (5-8) are aimed at healthcare professionals and should help them deliver better clinical care with more effective and safe use of AIT. Professionals still need to utilize their clinical training, experience and judgment to deliver personalized healthcare. The Guidelines provide answers to key clinical questions (see Box 1) summarizing the evidence for and against different therapies. Recommendations are clearly described but may not be appropriate for all people, patients and situations. A key conclusion from the Guidelines is the need to limit practice to the use of high quality, standardized AIT products with good evidence of effectiveness - a product-specific approach - since many available products are not supported by sufficient evidence of efficacy.

Future challenges

The use of AIT is currently restricted by the limited availability of high quality, standardized products with good evidence of effectiveness (9,10). This could be improved with the widespread adoption by industry and specialists of the best regulatory framework. Special consideration will however be required for rare allergens where it may not be possible to undertake large clinical trials. Another key limitation is access to AIT. Greater awareness of the need for and availability of AIT within primary care and partnership with specialists will be necessary to overcome this (11). Clinical care pathways and better quality standards of care are required to facilitate this. The Guidelines highlight many gaps in the evidence base, particularly around the longterm effectiveness of AIT, the evidence for effectiveness of many commercial products and a shortage of data in children and for health economic considerations. We hope that these Guidelines will catalyze the commissioning of research to fill these evidence gaps. EAACI plans to update these guidelines with recommendations informed by evidence published over the five years 2017-2022.

The AIT Guidelines and underpinning systematic reviews can all be accessed at

<http://www.eaaci.org/resources/guidelines/ait-guidelines-part-2.html> (last accessed 17th January 2018).

Acknowledgments

The EAACI Guidelines Group thank Stefan Vieths and Andreas Bonertz for their advice; all the Taskforce members, particularly the representatives from the patient organizations; the expert reviewers for their constructive appraisal of the draft guidelines; and members of EAACI who commented on the draft guidelines posted on the EAACI web site. We also thank EAACI and the BM4SIT project (grant number 601763) in the European Union's Seventh Framework Programme FP7 for their funding of the project.

Contributions

Antonella Muraro, Graham Roberts, Susanne Halken, Liz Angier, Montserrat Fernandez-Rivas, Roy Gerth van Wijk, Giovanni Pajno, Oliver Pfaar, Dermot Ryan, Gunter Sturm, Ronald van Ree, Eva-Maria Varga, Iona Agache, Marek Jutel, Susanne Lau and Aziz Sheikh were the AIT Guidelines Chairs. Claus Bachert, Moises Calderon, G Walter Canonica, Stephen Durham, Hans-Jørgen Malling and Ulrich Wahn all assisted in the finalization of the Guidelines after the public consultation. The EAACI Guidelines on AIT were chaired by Antonella Muraro and coordinated by Graham Roberts.

Box 1. Key points from each guideline

Prevention (5)

- A three year course of Allergen Immunotherapy (AIT) (subcutaneous immunotherapy [SCIT] or sublingual immunotherapy [SLIT]) can be considered in children with moderate to severe allergic rhinitis and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for short-term (i.e. up to 2 years post-treatment) (Grade A) and possibility long-term (Grade B) prevention of asthma symptoms in addition to improving the control of AR.
- Only AIT products with documented effect in patients with the relevant pollen allergy should be used and a product-specific evaluation of clinical efficacy and preventive effects is recommended.
- Before initiating AIT, the possible benefits including the beneficial effects of

controlling allergic rhinitis symptoms and the asthma preventive effect, disadvantages, potential harms, patients' preferences (SCIT or SLIT-tablets/ SLIT-drops), patients' adherence to treatment and costs should be discussed with the patient / family on an individual basis.

- There is an urgent need for more high-quality clinical trials on prevention in AIT.

Venom (6)

- Venom immunotherapy (VIT) is indicated in venom allergic individuals following moderate to severe systemic reactions (Grade A for adults, B for children).
- VIT is also recommended to reduce systemic allergic reactions in adults with skin symptoms only when quality of life is impaired (Grade A).
- VIT is safe for patients with special conditions, such as mastocytosis (Grade C).
- Pre- treatment with H1 antihistamines should be used to prevent large local reactions (Grade A).
- A 12-week maintenance injection interval can be recommended in life-long VIT (Grade C).
- A 200µg maintenance dose should be used for patients still reacting while on a conventional (100µg) dose (Grade C).
- Life-long VIT can be recommended in patients at high risk for relapse (Grade C).
- Considerable gaps were identified in the evidence base emphasizing the need for future well-designed studies, particularly in the paediatric population.

IgE-mediated food allergy (7)

- Allergen Immunotherapy for food allergy (FA-AIT) should only be performed by experienced personnel in research centers or in clinical centers with an extensive experience in food allergy AIT.
- Food allergy allergen immunotherapy (FA-AIT) should be considered for children from around 4 - 5 years of age with a persistent IgE-mediated food allergy to cow's milk (Grade A), hen's egg (Grade B) or peanut (Grade A) to increase the threshold of reactivity while on therapy. A benefit post-discontinuation is suggested but not confirmed.
- Oral immunotherapy (OIT) affords better efficacy than sublingual immunotherapy (SLIT) but OIT is associated with higher frequency of adverse events than SLIT

although most are not severe.

- The initial FA-AIT dosage and each increased dosage during the build-up phase should be performed in clinical setting.
- Patients and their families should be provided with information about the use of AIT for IgE-mediated food allergy to allow them to make an informed decision about the therapy (Grade D).
- Longitudinal, prospective, well-designed studies are needed to fill the many gaps yet to be addressed with the final goal of extending FA- AIT protocols in clinical practice as standard medical therapy.
- There is a paucity of evidence for use of FA-AIT in adults.

Allergic rhinoconjunctivitis (8)

- AIT should be considered in patients with allergic rhinitis (AR), with or without conjunctivitis; evidence of IgE-sensitization to one or more clinically relevant allergens; and moderate-to-severe symptoms despite regular and/or avoidance strategies.
- An individual product-based evaluation of evidence for efficacy is recommended before treatment with a specific product is initiated.
- The following can be recommended for AR for short-term benefit:
 - Continuous SCIT for seasonal (Grade A for adults, B for children) or perennial (Grade B for adults, C for children) allergens.
 - Pre- and pre-/co-seasonal SCIT (Grade A for adults, B for children).
 - Modified (allergoids) and unmodified allergen SCIT extracts (Grade A for adults, B for children).
 - SLIT aqueous solutions for grass and tree pollens (Grade B for adults, A in children).
- The following can be recommended for AR for short- and long-term benefit:
 - Continuous grass pollen SCIT (Grade A for adults, B for children).
 - Continuous grass pollen SLIT tablets or SLIT solution (Grade A).
 - HDM SLIT tablet (but not aqueous solution) for short-term (Grade A) and

long-term benefit (Grade B for adults, C for children).

- To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used (Grade A).
- SCIT and initial SLIT dosage should be administered by competent staff with patients waiting in the clinic for at least 30 minutes after dose (Grade C).
- Many gaps in the evidence base exist, particularly around long-term benefit and use in children.

Grades A to D represents the strength of the recommendation with A being the strongest with recommendations being based on consistent, randomized, controlled trial data; B being based on two groups, non-randomized studies (e.g., cohort, case-control); C being based on one group, non-randomized studies (e.g., before and after); and D being based on expert opinion (4).

Box 2. How can we facilitate the implementation of AIT Guidelines?

Improving access to Allergen Immunotherapy (11)

- Education and training for primary care personal in clinical allergy, including Allergen Immunotherapy (AIT).
- Stratifying patients into those who can be managed exclusively in primary care and those with more problematic disease who need referral to specialist care.
- Development of clinical care pathways and better quality standards of care to facilitate integrated care systems between primary and specialist care providers.

Regulation of allergen products (9,10)

- Improved and standardized definitions for future AIT trials.
- Harmonization of the regulations that are applied across Europe to promote the use of AIT products with proven quality, safety and efficacy.
- Special considerations for rare allergens where it is not viable to undertake very large RCTs to demonstrate efficacy and safety of AIT with the product.
- Improved analytical procedures to enable more precise characterizations of allergen products to ensure standardization of AIT formulations.

References

1. National Guideline Clearinghouse Expert Commentaries: A perspective on the Guidelines International Network and the Institute of Medicine's proposed standards for guideline development (<http://1.usa.gov/1anT6tu>)

2. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839–E842.
3. Brown GP. Evidence-based clinical practice guideline development: Principles, challenges, and accountability to evidence. *Journal of Surgical Oncology* 2010;101:1–2
4. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. 2013. <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/> Last accessed 27 July 2017.
5. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol*. 2017 Sep 13. doi: 10.1111/pai.12807.
6. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*. 2017 Jul 27. doi: 10.1111/all.13262.
7. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy*. 2017 Sep 27. doi: 10.1111/all.13319.
8. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. 2017 Sep 23. doi: 10.1111/all.13317.
9. Bonertz A, Roberts G, Slater JE, Bridgewater J, Rabin RL, Hoefnagel M, et al. Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States: An analysis from the EAACI AIT Guidelines Project. *Allergy*. 2017 Nov 17. doi: 10.1111/all.13357
10. Bonertz A, Roberts GC, Hoefnagel M, Timon M, Slater JE, Rabin RL, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: A global perspective on the regulation of allergen products. *Allergy*. 2017 Aug 3. doi: 10.1111/all.13266.
11. Ryan D, Gerth van Wijk R, Angier E, Kristiansen M, Zaman H, Sheikh A, et al. Challenges in the implementation of the EAACI AIT guidelines: A situational analysis of current provision of allergen immunotherapy. *Allergy*. 2017 Aug doi: 10.1111/all.13264